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Attorney Docket No.: **PENN-0701**

Inventors: **Alain H. Rook**

Serial No.: **09/419,328**

Filing Date: **October 15, 1999**

Examiner: **J. Dong**

Group Art Unit: **1646**

Title: **Methods for Treatment of Cutaneous T-Cell Lymphoma**

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Dear Sir:

REPLY BRIEF

I. ClaimsAppealed

The claims included in Appendix I of Appeal Brief were the proposed amended claims in response to the Final Rejection. Attached hereto is the pending claim set now under appeal. The amendments proposed in response to the Final Office Action were not entered.

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II. Response to the Examiner's Comments on the Issues on Appeal

The issues on appeal include: 1) whether claim 1 is anticipated under 35 U.S.C. 102(b) by Rook et al. (1997); 2) whether claims 1 and 3 are unpatentable under 35 U.S.C. 103(a) over Rook et al. (1996) in view of Verbik et al. (1996); 3) whether claim 3 is unpatentable under 35 U.S.C. 103(a) over Rook et al. (1996) and Verbik et al. (1996) and further in view of Rook et al. (1997); and 4) whether claim 4 is unpatentable under 35 U.S.C. 103(a) over Rook et al. (1996).

Issue: Whether claim 1 is anticipated in light of Rook et al. (1997)

The Examiner suggests that this paper teaches the clinical application of IL-12 to treat human cutaneous T cell lymphoma and provides a reasonable expectation of success because the method is not directed to a new use and the claim does not require that a specific result be attained. The Examiner has also dismissed a declaration provided by the inventor and author of this reference (Dr. Alain Rook) as being ineffective to overcome this rejection because it does not establish a reduction to practice of the invention prior to the effective date of the prior art reference,

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and further does not provide evidence that clinical efficacy was disclosed only after the publication of Rook et al. (1997).

As discussed in detail in the Appeal Brief, Rook et al. (1997) does not teach the successful and effective *in vivo* use of IL-12, either with or without interferon- γ , to treat cutaneous T cell lymphoma in humans. There is only a single statement in this paper that indicates "these studies led to a phase I trial of IL-12 to treat CTCL". No actual data on such a trial are provided or discussed. Additionally, the paper fails to provide details of how such a trial would be conducted.

Although the Examiner suggests that this single statement alone is sufficient for one of skill to know to design a clinical study using IL-12 with interferon- γ to treat CTCL in humans, the Examiner has not considered all of the steps that go into such design. A general level of operability is required in a reference to establish a *prima facie* case of obviousness or anticipation. See MPEP 2121. In accordance with MPEP 2121.01, the test in determining that quantum of prior art disclosure which is necessary to declare an applicant's invention "not novel" or "anticipated" within section 102, is whether a reference contains an "enabling disclosure". *In re Hoeksema*, 399F.2d 269 (CCPA 1968). A reference contains an "enabling

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disclosure" if the public was in possession of the claimed invention before the date of invention. Rook et al. (1997) do not provide data showing treatment in humans. It was not until after the publication at issue that the clinical efficacy of IL-12 in cutaneous T cell lymphoma patients was shown. This fact was stipulated in a declaration by the inventor, Dr. Alain Rook (see Appendix 3 of the Appeal Brief). Specifically, as stated at page 2, top paragraph, lines 3-9, although the 1997 paper states that clinical trials were underway, they were actually only in the planning stages in 1997 at the time of publication of the prior art reference. Since the inventor of the application was also the author of the prior art reference, his statements alone should be adequate evidence of what work had actually been done. At that time in 1997, and as specifically declared by Dr. Rook, "no patients had yet actually participated in the study." Therefore, contrary to the Examiner's suggestion, this declaration provides evidence that the clinical study had not been performed and that IL-12 had not yet been shown to be effective as a treatment for cutaneous T cell lymphoma. Accordingly, Rook et al. (1997) can not anticipate the instant invention of claim 1 which is drawn to treatment of advanced cutaneous T cell lymphoma. It is only with the specification in

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hand that describes results of treatment of humans that one of skill would be enabled to practice the claimed invention.

Therefore, based on the requirements of MPEP 2131, the paper by Rook et al. (1997) fails to anticipate the instant invention.

Issue: Whether claims 1 and 3 are obvious under 35 U.S.C. 103(a) over Rook et al. (1996) in view of Verbik et al. (1996)

The Examiner suggests that Rook et al. (1996) demonstrate that depressed interferon- γ production is normalized *in vitro*, indicating that a marked defect in IL-12 production by peripheral blood mononuclear cells in Sezary syndrome may be an important factor in the failure to produce normal amounts of interferon- γ and mediating normal cell-mediated immunity. The Examiner acknowledges that Rook et al. (1996) do not teach a method of *in vivo* treatment but then asserts that Verbik et al. (1996) teach a method of treatment of a murine lymphoma with IL-12 in mice, providing for a reasonable expectation of success in treating lymphoma in humans. The Examiner also suggests that the requirement of a reasonable expectation of success does not rest

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on a complete certainty of success and that virtually all clinical applications are based on *in vitro* and/or *in vivo* animal studies such as provided by Verbik et al. (1996).

As discussed in detail in the Appeal Brief, Rook et al. (1996) is a paper by the inventor that describes early studies with IL-12 in cells. As acknowledged by the Examiner, this paper does not teach treatment of advanced cutaneous T cell lymphoma in humans using IL-12 either alone or in combination with agents that increase interferon- γ production as claimed in claims 1 and 3. Verbik et al. (1996) teach the administration of IL-12 to mice suffering from liver lymphoma. Even as such, the use of IL-12 with other interleukins caused unexplained early deaths in the test mice. The paper further teaches that the mechanisms through which the IL-12 mediates *in vivo* anti-tumor responses is not fully understood. One of skill reading this paper would learn that even though early deaths occurred in groups of animals receiving combined treatments, the authors of this reference believed that it was IL-12 that was leading to unacceptable toxicity. Therefore, contrary to the Examiner's assertions at page 14 of the Examiner's Reply, the authors have definitively linked toxicity to IL-12, even though the effects were seen in combined treatment groups. One of skill would take the authors

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at their word and thus there would be an expectation of toxicity with use of IL-12 that could lead to unacceptable risks in humans.

Contrary to the Examiner's suggestions, Verbik et al. (1996) has put into question the safe use of IL-12 by showing that there was unexpected toxicity in animals that they specifically have attributed to IL-12. The fact that Verbik et al. (1996) teach that early deaths resulted with use of IL-12 in animals, not just a minor toxic effect but a life-threatening one, indicates that the use of IL-12 in conjunction with other therapeutics especially needs to be shown to be safe before testing in humans is begun. Therefore, the reference of Verbik et al. (1996) does not provide one of skill with a reasonable expectation of success for use of IL-12 in humans as an effective treatment for advanced cutaneous T cell lymphoma.

Specifically with respect to claim 3 and in response to the Examiner's suggestions at page 15 of the Examiner's Reply that one cannot conclude that IL-12 was leading to unacceptable toxicity in light of a showing of efficacy with IL-12 in this reference, Appellants respectfully point out that it is a general principle of pharmacology and toxicology that when two agents are combined, as is claimed in the claims under appeal, the toxicity

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of either agent can be very different than the toxicity of either agent alone. This is because one of skill cannot predict whether there will be additive toxicity or maybe even protection from toxicity when two agents are combined.

Accordingly, neither of the cited prior art references provide one of skill in the art with a reasonable expectation of successfully treating advanced cutaneous T cell lymphoma in a human via administration of IL-12 either alone or in combination with an adjunct therapeutic agent. In addition, there is no suggestion or teaching in the cited references to combine reference teachings as required. On the contrary, one of skill would refrain from administering IL-12 to humans based on the teachings of Verbik et al. (1996) and Rook et al. (1996) as combined by the Examiner. As a result, these references fail to establish a prima case of obviousness under 35 U.S.C. 103(a).

Issue: Whether claim 3 is obvious under 35 U.S.C. 103(a) in light of Rook et al. (1996) and Verbik et al. (1996) and further in view of Rook et al. (1997)

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The Examiner suggests that Rook et al. (1996) demonstrate that depressed interferon- γ production is normalized *in vitro*, indicating that a marked defect in IL-12 production by PBMCs in Sezary syndrome may be an important factor in the failure to produce normal amounts of interferon- γ and mediating normal cell-mediated immunity. The Examiner acknowledges that Rook et al. (1996) do not teach a method of *in vivo* treatment but then asserts that Verbik et al. (1996) teaches a method of treatment of a murine lymphoma with IL-12 in mice, providing for a reasonable expectation of success in treating lymphoma in humans. The Examiner then suggests that it would have been obvious for one of skill to make a composition comprising a recombinant IL-12 and interferon- γ or a retinoid in order to practice the method of claim 3 because Rook et al. (1997) establish that IL-12 is being studied in a Phase I clinical trial.

As with the issues discussed above, Appellant's respectfully disagree with the Examiner concerning the teachings of Rook et al. (1997) and Verbik et al. (1996).

In particular, and as discussed *supra*, Appellant's assert that Verbik et al. (1996) teach an unexpected toxicity of IL-12 when it is combined with other treatments *in vivo*. Since claim 3 is a combined treatment claim of IL-12 with another agent, the

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teachings of Verbik et al. (1996) are directly relevant and would teach one of skill that combining IL-12 with other agents *in vivo* can lead to unacceptable toxicity. Therefore, one of skill would not have an expectation of success nor a motivation to practice the claimed invention of claim 3 based on the teachings of Verbik et al. (1996).

With respect to Rook et al. (1997), this paper is a review of the literature that supported a role for marked defects in interleukin-12 (IL-12) production in the pathogenesis of cutaneous T cell lymphoma. Nowhere does this paper provide data showing the successful and effective *in vivo* use of IL-12, either with or without interferon- γ , to treat cutaneous T cell lymphoma in humans. There is only a single statement in this paper that indicates "these studies led to a phase I trial of IL-12 to treat CTCL". No actual data on such a trial are provided or discussed. Additionally, the paper fails to provide details of how such a trial would be conducted. Therefore, this paper cannot support an expectation of success for *in vivo* treatment in humans of a combined IL-12 treatment regimen since. Further, as discussed in the declaration by the inventor (Appendix 3 of the Appeal Brief), the clinical studies were not actually underway at the time of

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publication of the paper and were, in fact, only in the planning stages. It is only with the specification in hand that one of skill is provided with actual evidence of efficacy of the instant invention.

As discussed *supra*, a general level of operability is required in a reference to establish a *prima facie* case of obviousness or anticipation. See MPEP 2121. In accordance with MPEP 2121.01, the test in determining that quantum of prior art disclosure which is necessary to declare an applicant's invention obvious within section 103, is whether a reference contains an "enabling disclosure". *In re Hoeksema*, 399F.2d 269(CCPA 1968). A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. At that time in 1997 of publication of the paper by Rook (1997), and as specifically declared by Dr. Rook, "no patients had yet actually participated in the study." Therefore, contrary to the Examiner's suggestion, this declaration provides evidence that the clinical study had not been performed and that IL-12 had not yet been shown to be effective as a treatment for cutaneous T cell lymphoma. It is only with the specification in hand that describes results of treatment of humans that the invention was enabled.

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As a result, the cited combination of prior art references fails to meet all of the obviousness criteria (teaching of all limitations through a reduction to practice, motivation and an expectation of success) with respect to the instant invention of claim 3. None of the cited prior art references provide one of skill in the art with a reasonable expectation of successfully treating advanced cutaneous T cell lymphoma in a human with administration of IL-12 alone or in combination with an adjunct therapeutic agent that stimulates interferon- γ production. As acknowledged by the Examiner, Rook et al. (1996) do not teach a method of *in vivo* treatment using IL-12. Further, Rook et al. (1996) fail to teach administration of IL-12 even *in vitro* with an adjunct therapeutic agent as claimed in claim 3. Verbik et al. (1996) actually put into question the safe use of IL-12 by showing that there was unexpected toxicity in animals that they attributed to IL-12. Finally, Rook et al. (1997) do not teach use of IL-12 with adjunct therapeutic agents in a clinical trial, as shown by the declaration provided by the inventor. Therefore, based on the requirements of MPEP 2143, this combination of prior art fails to make obvious the instant invention of claim 3.

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**Issue: Whether claim 4 is obvious under 35 U.S.C. 103(a) in
light of Rook et al. (1996).**

The Examiner suggests that although Rook et al. (1996) do not teach a method of *in vivo* treatment, it would have been *prima facie* obvious for one of ordinary skill to design a method for treatment of cutaneous T cell lymphoma based on the teaching of Rook et al. (1996) and the suggestions that Sezary syndrome, an advanced form of lymphoma, is characterized by marked depression of interferon- γ production and a defect in IL-12 production by PBMCs. Further, the Examiner suggested that one of skill would have been motivated to treat cutaneous T cell lymphoma by administering IL-12 with an adjunct agent that stimulates interferon- γ production at Rook's suggestion and would have reasonably expected success because such combinations would correct both defects in these patients. The Examiner acknowledges that the reference is silent about a pharmaceutically acceptable carrier but that this is well known in the art.

Rook et al. (1996) is a paper by the inventor of the present application that describes early studies with IL-12 in cells.

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This paper does not teach treatment of advanced cutaneous T cell lymphoma in humans using IL-12 in combination with agents that increase interferon- γ production as claimed in claim 4.

The Examiner suggests in the Reply that since claim 4 does not specify what the composition of contains, Rook et al. (1996) makes this claim obvious in indicating that treatment with IL-12 either alone or with other Th1-inducing agents should be pursued. The Examiner suggests that interferon- γ is a TH1 cytokine. Appellants respectfully point out that this reference, however, does not teach or suggest the use of agents that "stimulates interferon- γ production", language that is directly in claim 4.

To establish a *prima facie* case of obviousness under 35 U.S.C. 103(a) three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all the claim limitations.

The cited combination of prior art references fails to meet all of these criteria with respect to the instant invention of claim 4. None of the cited prior art references provide one of

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skill in the art with a reasonable expectation of successfully treating advanced cutaneous T cell lymphoma in a human with administration of IL-12 in combination with an adjunct therapeutic agent that stimulates interferon- γ production. Rook et al. (1996) do not teach a composition comprising recombinant IL-12 with a separate adjunct agent that stimulates production of interferon- γ , as is disclosed and claimed in the instant invention of claim 4. Further, MPEP 2143 and the Courts are quite clear; both the teaching and suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on applicant's disclosure. *In re Vacek*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The cited prior art fails to provide this reasonable expectation of success, as well as teaching or suggesting compounds that stimulate interferon- γ production specifically. It is only with the instant specification in hand, which demonstrates the efficacy of Applicant's invention that one of skill has a reasonable expectation of success or has an understanding of the kinds of agents that could be used to stimulate interferon- γ

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production. Accordingly, the cited prior art fails to establish a *prima facie* case of obviousness as set forth in MPEP 2143.

Respectfully submitted,

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Claims that are on Appeal

1. A method for treatment of advanced cutaneous T cell lymphoma in a human comprising administering to a human an effective amount of recombinant interleukin-12 in a pharmaceutically acceptable carrier.

3. A composition for treatment of advanced cutaneous T cell lymphoma in a human comprising recombinant interleukin-12 and an adjunct therapeutic agent which stimulates interferon- γ production, said adjunct therapeutic agent comprising a retinoid, interleukin 18, interferon- α or interferon- γ .

4. A method for treatment of advanced cutaneous T cell lymphoma in a human comprising administering to a human an effective amount of recombinant interleukin-12 in a pharmaceutically acceptable carrier and an adjunct therapeutic agent which stimulates interferon- γ production.

APPENDIX 1

1. A method for treatment of advanced cutaneous T cell lymphoma in a human comprising administering to a human 100 to 300 ng/ml of recombinant interleukin-12 in a pharmaceutically acceptable carrier.

3. A composition for treatment of advanced cutaneous T cell lymphoma in a human comprising a solution of 100 to 300 ng/ml of recombinant interleukin-12 and an adjunct therapeutic agent which stimulates interferon- γ production, said adjunct therapeutic agent comprising a retinoid, interleukin 18, interferon- α or interferon- γ .

4. A method for treatment of advanced cutaneous T cell lymphoma in a human comprising administering to a human 100 to 300 ng/ml of recombinant interleukin-12 in a pharmaceutically acceptable carrier and an adjunct therapeutic agent which stimulates interferon- γ production.

APPENDIX 2

Antitumor effects of IL-12 against residual lymphoma

Table 4. Cytotoxic effector cell activity and frequency of NK cells in residual lymphoma-bearing IL-12-treated BALB/c mouse spleen

Experimental group	Baseline cytotoxicity ^a	Lytic units/spleen ^b	IL-2 ASC cytotoxicity ^a	LAK precursor cell/spleen ^b
BMT only	0.23	38	1.20	193
BMT + H10 + IL-2-ASC	0.0	0.0	0.48	69
BMT + H10 + IL-2-ASC + IL-12	0.33	113	0.95	332
BMT + H10 + IL-12	0.41	100	0.98	236
Untreated H10-bearing controls	0.75	185	11.87	2931
Untreated normal controls	1.65	271	9.50	1562

^a Values are expressed as lytic units.^b Lytic units and LAK precursor cells per spleen were calculated by dividing the total spleen cellularity by the number of effector cells equal to 1 lytic unit.

also performed to investigate the effects of IL-12 administration on immunohematological reconstitution following BMT. Similar studies were performed using syngeneic spleen cells as the hematopoietic stem cell source. However, the bone marrow cells appeared to be better from a therapeutic standpoint when used in combination with cytokine therapy. One of the major obstacles in developing immunologically based therapies for the treatment of MRD is overcoming the impaired immune system in the host following hematopoietic stem cell transplantation. Adjuvant therapy with biological response modifiers such as recombinant cytokines, which may accelerate effector cell recovery or activate antitumor immune functions, is one possible method for overcoming immune suppression during the initial period after BMT. Another approach is to intravenously infuse antitumor effector cells that have been previously activated with cytokine or some other biological response modifier for augmenting their antitumor activity. The utilization of effector cells activated with IL-2 for mediating antitumor activity in both mice and humans has been reported [19-21]. The utilization of IL-2-activated NK cells for controlling MRD following HDT and autologous peripheral blood stem cell transplantation (PBSCT) was reported by Lister *et al.* [22]. They found that infusion of IL-2-activated autologous NK cells together with continuous i.v. IL-2 administration following HDT-PBSCT coincided with increased NK activity in the patients' blood. In our study, IL-2-ASC were injected into lymphoma-bearing mice following lethal TBI and BMT as a single therapeutic agent or together with IL-12 administration. Since IL-12 is known to stimulate the growth and cytotoxic activity of NK cells *in vivo*, by combining activated spleen cells with IL-12 administration, we hoped that their

antitumor reactivity would be enhanced. The results from these studies showed that there was no therapeutic advantage using IL-2-ASC in combination with IL-12, based on the animals' overall survival. Rather, this combination resulted in early deaths for some of the mice when compared to the mice receiving IL-2-ASC alone or IL-12 alone. However, evaluation of the liver tumor burden in the mice treated with either IL-12 alone or IL-12 combined with IL-2-ASC on day +11 post BMT revealed a marked reduction in their tumor burden when compared to the mice treated with IL-2-ASC alone (Figure 4). It is not clear why both IL-2-ASC and IL-12 caused early deaths for some of the mice. One explanation may be that IL-12 induced the secretion of inflammatory cytokines such as IFN- γ from the IL-2-ASC, damaging the animals' gastrointestinal tissues. Recently, Neta *et al.* observed that lethally irradiated mice treated with IL-12 had severe gastrointestinal damage that was much more pronounced than the damage induced by radiation alone [23]. However, when the mice were treated with anti-IFN- γ Ab, damage to the gut was abrogated.

Currently, the mechanism(s) through which IL-12 mediates *in vivo* antitumor responses is not fully understood. IL-12 is known to have a significant role in regulating immune function, either by direct activation of effector cells or indirectly by stimulating secretion of other cytokines. IL-12 is a potent inducer of IFN- γ secretion by NK cells and T lymphocytes [8, 24]. Furthermore, IL-12 promotes the proliferation and cytolytic maturation of CTL clones as well as augmenting the cytolytic activity of NK cells and T lymphocytes *in vivo* [8, 24, 25]. In the transplantation studies reported here, the suppression of tumor cell growth in the livers of the IL-12-treated mice might be due to the augmentation of liver-associated NK

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